AMENDMENTS TO THE SPECIFICATION

At page 1, please insert the following new heading and paragraph after the Title of the Invention and prior to paragraph [0001]:

PRIORITY CLAIM

This application is a 35 U.S.C. §371 National Phase filing of PCT Application No. PCT/US04/015934 filed 19 May 2004, which application claimed priority of the following commonly owned U.S. Provisional Patent Application – U.S.S.N. 60/471,639, filed 19 May 2003. The PCT application designated the United States and was published in the English language on 2 December 2004 as WO 04/104457 A2.

At page 4, please cancel paragraphs [0037] and [0048].

At page 4, please amend paragraphs [0038] – [0047] as follows:

FIGS. ~~13A-13F~~ 7A–7F present schematic representations and graphical representations of two approaches for conducting electric field gradient focusing in accordance with certain examples of the devices and methods disclosed here;

FIG. [[14]] 8 is a schematic drawing of another example of a device in accordance with the present disclosure;

FIGS. ~~15A and 15B~~ 9A and 9B each is a graphical representation of the field strength profile and potential profile, respectively, of a linear field gradient (15.5 v/cm.sup.2) in accordance with another example of the methods and devices disclosed here;

FIG. [[16]] 10 is a schematic representation of the resistance between two adjacent electrodes in another example of the methods and devices disclosed here;

FIG. [[17]] 11 is a schematic diagram of a representative electric field gradient focusing gradient control model of an example of the methods and devices disclosed here;

FIG. [[18]] 12 is a schematic diagram of a representative electric field gradient focusing gradient control circuits;

FIG. [[19]] 13 is a circuit diagram of a representative controller unit;

FIG. [[20]] 14 is a circuit diagram of a representative controller unit;

FIG. [[21]] 15 is a schematic illustration of a representative DAC board circuit diagram illustrating connections;

~~FIG. 22 is a~~ FIGS. 16A and 16B are schematic illustrations of representative DAC board circuit diagrams illustrating components;

At page 5, please amend paragraphs [0049] – [0051] as follows:

~~FIG. 25 is a~~ FIGS. 17A–C are schematic illustrations of representative configurations for other examples of the device;

FIGS. ~~26a-26c~~ 18a-18c show use of the bulk fluid flow gate for an exemplary separation.

FIGS. ~~27a-27b~~ 19a-19b show use of the bulk fluid flow gate for another exemplary separation.

At page 5, please amend paragraph [0056] as follows:

In certain examples, bulk fluid 5 is introduced into the first chamber 2 through first entry port 2b (see FIG. 1b). Introduction of bulk fluid results in substantially greater hydrodynamic resistance downstream of first entry port 2b such that the hydrodynamic resistance at first exit port 2d is greater than the hydrodynamic resistance at second exit port 2a. Fluid flow 6, which is upstream [[or]] of first entry port 2b typically is of a lower volume and/or velocity than bulk fluid flow 5 such that the hydrodynamic resistance at second exit port 2a is substantially less than the hydrodynamic resistance at first exit port 2d. Sample 7 is introduced into first chamber 2 through second entry port 2c.

At page 5, please amend paragraph [0058] as follows:

In certain examples, first entry port 2e can be positioned at an obtuse angle to the axial direction of first chamber 2 (see FIG. 1c). A result of such positioning of first entry port 2e at an obtuse angle is that bulk fluid is directed substantially towards first exit port 2d. First exit port 2d experiences greater hydrodynamic resistance [[that]] than second exit port 2a, which is upstream of first entry port 2e. The velocity of fluid 6, which is upstream of first entry port 2e, is substantially lower than the velocity of bulk fluid flow 5, and fluid 6 flows in a substantially opposite direction to bulk fluid 5. The gating effect is substantially reduced once analyte migrates upstream of first entry port 2e.

At pages 5-6, please amend paragraph [0061] as follows:

In certain examples, the first chamber of the bulk fluid flow gate includes a non-uniform cross-sectional flow channel, that is to say, the cross-sectional area of the separation chamber varies axially along the channel. For example, FIG. 1d shows a first chamber that has a non-uniform cross-sectional flow channel. The cross-sectional area of the first chamber decreases from second entry channel 2c and towards first exit port 2d. FIG. 1e shows a non-uniform first chamber in which the cross-sectional area decreases from first entry port 2b towards second exit port 2a. FIG. 1f shows a non-uniform first chamber in which the cross-sectional area of first chamber decreases from first entry port 2b to second exit port 2a, and the cross-sectional area of the first chamber also decreases from second entry port 2c towards first [[entry]] <u>exit</u> port 2d. [[FIG. 1f]] <u>FIG. 1g</u> shows a non-uniform first chamber in which the cross-sectional area decreases at a point between first entry port 2b and second entry port 2c. [[FIG. 1g]] <u>FIG. 1h</u> shows a non-uniform first chamber in which the cross-sectional area of the first chamber increases from first entry port 2b and towards second exit port 2a, and in which the cross-sectional area decreases from second entry port 2c towards first exit port 2d. The person of ordinary skill in the art, given the benefit of this disclosure, will be able to select these and other non-uniform chambers for an intended use of the bulk fluid flow gate. The first chamber in certain examples has a substantially uniform height (height here meaning the direction normal to the plane of the membrane) and a non-uniform or non-constant width (width here meaning the direction perpendicular to the overall direction of flow and parallel to the plane of the membrane). In other examples, the first chamber has a substantially uniform width and a varying or non-uniform height. Yet other examples employ a first chamber of non-uniform width and non-uniform height. Other examples include a first chamber defined by one or more non-linear walls, for example, a series of faces or facets, some or all having non-uniform dimensions; or wherein the first chamber has a curved cross-section, such as, for example, a half-circular cross-section, that varies axially, as, for example, a half-cone-shaped chamber.

At page 8, please amend paragraphs [0081] – [0082] as follows:

First block 110 includes conduits 114 and 116 which terminate in opposing ends of trough 112. Conduits 114 and 116 serve as the first exit port and the second exit port. First block 110 further includes channel 430 which terminates in trough 112 and which provides for introduction of bulk fluid into the device. Channel 436 also terminates in trough 112 and provides for introduction of sample into the first chamber. Other channels, e.g., channels 118 and 119, may be present for sampling. ~~Channels 118 and 119 also terminate in trough 112 and provide for removal and/or introduction of in the first chamber.~~ Second block 120 includes conduits 215 and 217, which terminate in opposing ends of trough 122. These conduits serve to introduce and exit liquid flow (e.g., coolant) through the electrode housing. In examples of the device that include an electrode pair in addition to the electrode array, second block 120 further includes channels 218 which terminate in trough 122. Channels 218 receive electrodes 220 and 223, which like the electrode array, are in electrical communication with liquid in the electrode housing when the device is in operation.

An example[[s]] of an assembled device is illustrated in FIGS. 4 and 5. Referring to FIG. 4, device 100 includes blocks 110 and 120 and sheets 130 and 140, and permeable member [[16]] 416. First entry port 320 includes adapter 320a, e.g., a connecting device. Second entry port 318 also includes an adapter 318a. First exit port 114 is positioned upstream of first entry port 320. Second exit port 116 is positioned downstream from first entry port 320. Optional sampling ports 118 are also shown. Connector 224 leads to the device's controller and provides current to the electrode(s) or the electrode array. The representative device further includes first and second plates 170 and 180, respectively, which overlie the outward surfaces of blocks 110 and 120, respectively. Plates 170 and 180 can reinforce the assembly. Plates 170 and 180 are preferably steel plates. The bulk fluid flow gate shown in FIG. 4 generally comprises a laminate structure. Suitable laminate structures, and methods

for making such laminate structures, are disclosed in the commonly assigned published PCT applications incorporated by referenced above.

At page 10, please amend paragraph [0090] as follows:

The control circuits are designed to manipulate the field gradient by adjusting the effective electrical resistance between two adjacent electrodes (see [[FIG. 16]] FIG. 10). In one example, each pair of electrodes is connected to one of the 50 controller units. A schematic of such an example is shown in [[FIG. 17]] FIG. 11, in which the blocks with dash line frames are controller units and each of the controller units handles the data acquisition and the resistance control of two adjacent electrodes.

At page 10, please amend paragraphs [0096] – [0099] as follows:

In certain examples, dynamic electric field gradients are created by a computer-controlled external circuit, which manipulates the field strength between each pair of adjacent electrodes, as exemplified in [[FIG. 14]] FIG. 8. Varying field strength along the first chamber can thus be achieved. ~~FIGS. 15A and 15B~~ FIGS. 9A and 9B are graphical representations of linear electric field gradients so generated.

Representative gradient control circuits are shown schematically in [[FIG. 18]] FIG. 12.

The blocks represent electronic boards, the lines represent standard ribbon cables, e.g., IDE cables, USB cables, IEEE1392 cables, serial cables, parallel cables, SATA cables, SCSI cables and the like. Referring to [[FIG. 18]] FIG. 12, the PC monitor/controller board and the 13-bit DAC board were built in our laboratory. Some modifications have been made for better performance. The data channels

between the two CIO-EXP32 boards and the CIO-DAS16Jr boards are programmed rather than being physically connected. CIO-DAS16Jr and CIO-DIO24 are plugged into extension slots of the PC. The two thermocouple boards CIO-EXP32, the 16-channel ADC board CIO-DAS16/Jr and the 24-channel Digital I/O board CIO-DIO24 were purchased from ComputerBoards, Inc. Standard SCSI ribbon cables are used to connect all the boards. There are 50 controller units plugged into the mother board. Each unit corresponds to one pair of electrodes. The whole system was grounded to protect the circuits from unexpected shock.

The gradient control is accomplished with PC-controlled circuits, diagrammed in [[FIG. 19]] <u>FIG. 13</u>, which are composed of electronic circuit boards. Pin 1 and 4 are connected to electrodes and neighboring units. The electrical potential on the electrode is reduced by 1/100, then enters amplifier LF411C where the load of the signal is increased. The signal is then sent to EXP32 board through pin 12, and the control signal (pin 10, 0-5 V) from the DAC board adjusts the current going through the optical isolator MCT275. A circuit diagram of the controller unit is shown in [[FIG. 20]] <u>FIG. 14</u>. A logic diagram for circuit diagram for ADC board is shown in [[FIG. 21]] <u>FIG. 15</u>. A circuit diagram for the ADC board with components identified is shown in [[FIG. 22]] <u>FIGS. 16A and 16B</u>.

At page 11, please amend paragraph [0102] as follows:

As noted above, the electrode housings can include more than one electrode array. For example, two electrode arrays can be associated with the first chamber in a configuration in which the first chamber is positioned in between the two arrays. Similarly, the first chamber can include, for example, four electrode arrays positioned about the first chamber in a quadrupole-type configuration. Representative devices including one, two, and four electrode arrays are illustrated schematically in [[FIGS. 25A-C]] <u>FIGS. 17A-C</u>. Referring to [[FIG. 25]] <u>FIG. 17</u>, representative device 10

including a single electrode array (i.e., located in electrode housing 14) and a first chamber (i.e., chamber 12) is shown in [[FIG. 25A]] FIG. 17A. ~~FIGS. 25B and 25C~~ FIGS. 17B and 17C illustrate representative devices 610 and 710 having two and four electrode arrays and electrode chambers 614 and 714 arranged about separation chamber 612 and 712, respectively.

At page 12, please amend paragraphs [0112] – [0112] as follows:

In certain examples and referring to ~~FIG. 26a~~ FIG. 18a, during operation of the bulk fluid flow gate, sample 6 is introduced into the first chamber 2 through second entry port 2c. In this example, the sample comprises a single charged analyte that is negatively charged. In the presence of an electric field, the sample will be driven towards positively charged electrode 3a and away from negatively charged electrode 3b.

In certain examples, the hydrodynamic force generated by bulk fluid and the driving force generated by the electric field are selected such that the sample is allowed to migrate towards second [[entry]] exit port 2a Without wishing to be bound by any particular scientific theory, the operating parameters in this example are selected such that upon arrival of the analyte at first entry port 2b, the hydrodynamic force and the driving force of the electric field are approximately equal so that no net migration of analyte 6a occurs (see ~~FIG. 26b~~ FIG. 18b). Impurities in the sample are allowed to migrate and exit the first chamber either through first exit port 2d or second exit port 2a. After exiting of impurities, the analyte can exit through the second exit port by increasing the electric field strength and/or reducing the hydrodynamic force generated by bulk fluid flow. In examples where it is desirable to exit the analyte from the first exit port, the hydrodynamic force can be increased or the electric field strength can be decreased so that the sample exits from the first exit port. It will be within the ability of the person of ordinary skill in the art to select suitable hydrodynamic forces and electric field strengths so that the analyte will exit

from either the first exit port [[of]] or the second exit port.

In other examples and referring to ~~FIG. 27a~~ FIG. 19a, during operation of the bulk fluid flow gate, sample 6 is introduced through second entry port 2c. In the example shown in ~~FIGS. 27a and 27b~~ FIGS. 19a and 19b, the sample comprises two analytes--one positively charged and one negatively charged. Bulk fluid 5 is flowed into chamber 2 and exits chamber 2 though first exit port 2d, which is downstream of first entry port 2b and second entry port 2c. The analytes typically will migrate towards the electrode having an opposite charge. One analyte of the sample will migrate towards electrode 3a and the other analyte of the sample will migrate towards electrode 3b. Without wishing to be bound by any particular scientific theory, because analyte 6b migrates in the same direction as bulk fluid flow, analyte 6b typically will exit the first chamber, through first exit port 2d, faster than analyte 6a will exit the first chamber. In particular, the driving force of the electric field should exceed the hydrodynamic force generated by bulk fluid flow for analyte 6a so that the analyte can migrate towards second exit port 2a. Depending on the selected hydrodynamic force and selected electric field strength, the migrating analyte can be halted at any portion in the chamber. In certain examples, the hydrodynamic force and electric field strength are selected such that once analyte 6a migrates to a position proximate first entry port [[6a]] 2b, the analyte is held in this position until a user desires to elute the analyte from the chamber through second exit port 2a. In certain examples, the analyte is held proximate to first entry port 2b until substantially all other analyte exits the chamber through first exit port [[2a]] 2d or second exit port 2a (see ~~FIG. 26c~~ FIG. 19c). Then, in certain examples, the hydrodynamic force is increased, or the electric field strength is decreased, and analyte 6a is pushed back downstream of the first entry port and exits through first exit port 2d. In other examples, the hydrodynamic force is decreased and/or the electric field strength is increased and analyte 6a exits the first chamber through second exit port 2a. It will be within the ability of the person of ordinary skill in the art to select suitable hydrodynamic forces and electric field strengths to elute analytes from a desired port.